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1: Hum Gene Ther. 1997 Jan 20;8(2):171-6.

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**Exogenous surfactant enhances the delivery of recombinant adenoviral vectors to the lung.**

Katkin JP, Husser RC, Langston C, Welty SE.

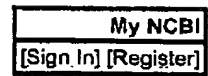
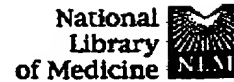
Department of Pediatrics, Baylor College of Medicine, Houston, TX 77030, USA.

Somatic gene therapy for pulmonary diseases must be accomplished in vivo, requiring the spread of a gene transfer vector across a vast expanse of respiratory epithelium. Surfactant, a naturally occurring protein and lipid mixture used to treat the respiratory distress syndrome of prematurity, disperses rapidly and evenly throughout the lung. We employed exogenous bovine surfactant (Survanta beractant) as a carrier vehicle for pulmonary delivery of a recombinant adenovirus expressing beta-galactosidase (beta-Gal). Rats treated with an adenovirus-beractant mixture demonstrated more uniform lobar distribution of transgene expression than rats treated with the same amount of virus in saline. Tissue homogenates were examined for quantitative beta-Gal expression by reaction with o-nitrophenol beta-n-galactopyranoside (ONPG). The degree of beta-Gal activity was affected by both the volume and type of carrier used to deliver the virus. At low volumes (0.5 ml, 1.3 ml/kg), beractant-treated animals demonstrated significantly greater pulmonary beta-Gal activity than saline-treated animals ( $p < 0.002$ ) and untreated controls. At high volume (1.2 ml, 4 ml/kg), average beta-Gal activity was similar between groups treated with beractant or saline, but was more variable within the saline treated group. Higher volumes of delivery medium were associated with increased levels of beta-Gal expression regardless of the carrier used. Survanta was well tolerated by the animals and did not affect the duration of transgene expression. Exogenous beractant provides a useful medium for delivering recombinant adenoviruses to the lung when diffuse distribution of transgene expression is desired.

PMID: 9017420 [PubMed - indexed for MEDLINE]

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1: J Biol Chem. 1997 Mar 7;272(10):6479-89.

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### Complexes of adenovirus with polycationic polymers and cationic lipids increase the efficiency of gene transfer in vitro and in vivo.

Fashender A, Zabner J, Chillon M, Moninger TO, Puga AP, Davidson BL, Welsh MJ.

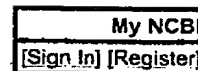
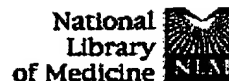
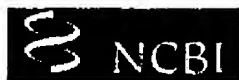
Howard Hughes Medical Institute, Department of Internal Medicine, University of Iowa College of Medicine, Iowa City, Iowa 52242, USA.

Improving the efficiency of gene transfer remains an important goal in developing new treatments for cystic fibrosis and other diseases. Adenovirus vectors and nonviral vectors each have specific advantages, but they also have limitations. Adenovirus vectors efficiently escape from the endosome and enter the nucleus, but the virus shows limited binding to airway epithelia. Nonviral cationic vectors bind efficiently to the negatively charged cell surface, but they do not catalyze subsequent steps in gene transfer. To take advantage of the unique features of the two different vector systems, we noncovalently complexed cationic molecules with recombinant adenovirus encoding a transgene. Complexes of cationic polymers and cationic lipids with adenovirus increased adenovirus uptake and transgene expression in cells that were inefficiently infected by adenovirus alone. Infection by both complexes was independent of adenovirus fiber and its receptor and occurred via a different cellular pathway than adenovirus alone. Complexes of cationic molecules and adenovirus also enhanced gene transfer to differentiated human airway epithelia in vitro and to the nasal epithelium of cystic fibrosis mice in vivo. These data show that complexes of adenovirus and cationic molecules increase the efficiency of gene transfer, which may enhance the development of gene therapy.

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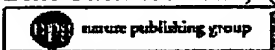
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1: Gene Ther. 1997 Jun;4(6):611-7.

[Related Articles, Links](#)**Antibody to CD40 ligand inhibits both humoral and cellular immune responses to adenoviral vectors and facilitates repeated administration to mouse airway.****Scaria A, St George JA, Gregory RJ, Noelle RJ, Wadsworth SC, Smith AE, Kaplan JM.**

Genzyme Corporation, Framingham, MA 01701, USA.

Adenoviral vectors have been used successfully to transfer the human CFTR cDNA to respiratory epithelium in animal models and to CF patients in vivo. However, studies done primarily in mice, indicate that present vector systems have limitations. Among other things, transgene expression in the lung is transient and the production of neutralizing antibodies against adenovirus correlates with a reduced ability to readminister a vector of the same serotype. Here we demonstrate that in mice, a transient blockade of costimulation between activated T cells and B cells/antigen presenting cells using a monoclonal antibody (MR1) against murine CD40 ligand inhibits the development of neutralizing antibodies to adenoviral (Ad) vector. MR1 also decreased the cellular immune response to Ad vector and allowed an increase in persistence of transgene expression. Furthermore, when administered with a second dose of Ad vector to mice preimmunized against vector, MR1 was able to interfere with the development of a secondary antibody response and allowed for high levels of transgene expression upon a third administration of vector to the airway.

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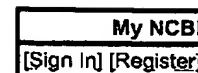
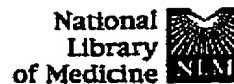
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1: Proc Assoc Am Physicians. 1996 Mar;108(2):165-72.

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**A model for keratinocyte gene therapy: preclinical and therapeutic considerations.**

Lu B, Scott G, Goldsmith LA.

Department of Dermatology, University of Rochester School of Medicine, NY 14642, USA.

Gene transfer to the skin is essential for correcting genetic disorders and studying skin biology. Previous attempts at in vivo gene transfer have employed replication-deficient adenovirus injected subcutaneously and plasmid DNA propelled by a gene gun. In this report, we used mouse skin as a model and evaluated the efficiency of these two methods. Using the luciferase reporter gene, we found that adenovirus injected subcutaneously transduced primarily cells in the dermis. However, particle bombardment of skin by gene gun delivered the reporter gene mainly into the epidermis. When mouse skin was bombarded with a DNA construct expressing human TGF-alpha, the epidermis of the treated mice showed localized epidermal acanthosis and hypergranulosis, which resembled the histological phenotype of previously described transgenic mice overexpressing TGF-alpha in the epidermis. These results suggest that the gene gun may be an effective tool for epidermal gene transfer and could be potentially useful in determining in vivo effects of growth factors and cytokines on the epidermis.

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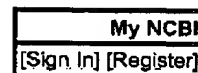
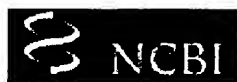
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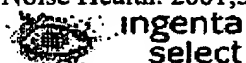
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1: Noise Health. 2001;3(11):37-47.

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**Gene-based therapy for inner ear disease.****Kawamoto K, Kanzaki S, Yagi M, Stover T, Prieskorn DM, Dolan DF, Müller JM, Raphael Y.**

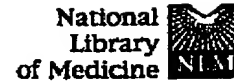
Kresge Hearing Research Institute, The University of Michigan Medical School, Ann Arbor, MI 48109-0648, USA.

Environmental inner ear insults often lead to hair cell injury and loss. Therapeutic measures for the prevention of hair cell loss are currently limited. Several reports have demonstrated the applicability of growth factors for hair cell protection. The goal of the experiments presented here was to assess the protective capability of the human GDNF transgene against noise trauma in the guinea pig cochlea. The left ears of guinea pigs were inoculated with a recombinant adenovirus with a human GDNF insert (Ad.GDNF). Four days later, animals were exposed to noise trauma. One week later, animals were sacrificed and hair cells counted in the left (inoculated) and right (non-inoculated) ears. Auditory brainstem thresholds were measured before the inoculation and just prior to sacrifice. Control groups included inoculation with a reporter gene vector (Ad.lacZ) and Ad.GDNF in normal ears with no noise exposure. The results show that intracochlear inoculation with adenovirus into normal ears does not compromise hair cell counts and ABR thresholds. Both Ad.GDNF and Ad.lacZ vectors can protect the cochlear hair cells and hearing from the noise insult. The difference between the protection afforded by Ad.GDNF and that of the Ad.lacZ vector is not statistically significant. The mechanism of Ad.lacZ protection needs to be elucidated. The data demonstrate the general feasibility of gene therapy for over-expression of neurotrophic factors against noise trauma, and emphasize the complexity of the technique and the problems of variability between subjects.

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1: J Clin Invest. 1997 Mar 1;99(5):1098-106.

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## Oral tolerization to adenoviral antigens permits long-term gene expression using recombinant adenoviral vectors.

Ilan Y, Prakash R, Davidson A, Jona, Droguett G, Horwitz MS, Chowdhury NR, Chowdhury JR.

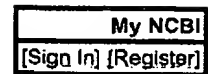
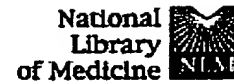
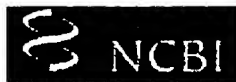
Department of Medicine, Albert Einstein College of Medicine, Bronx, New York 10461, USA.

Recombinant adenoviruses (Ads) efficiently transfer foreign genes into hepatocytes in vivo, but the duration of transgene expression is limited by the host immune response which precludes gene expression upon readministration of the virus. To test if this immune response can be abrogated by oral tolerization, we instilled protein extracts of a recombinant adenovirus type-5 via gastroduodenostomy tubes into bilirubin-UDP-glucuronosyltransferase-1 (BUGT1)-deficient jaundiced Gunn rats. Control rats received BSA. Subsequent intravenous injection  $5 \times 10^9$  pfu of a recombinant adenovirus-expressing human BUGT1 (Ad-hBUGT1) resulted in hepatic expression of human BUGT1 (hBUGT1) with reduction of serum bilirubin levels by 70%. After 2 mo serum bilirubin increased gradually. In orally tolerized rats, but not in controls, a second dose of the virus on day 98 markedly reduced serum bilirubin again. In the tolerized rats, the development of antiadenoviral neutralizing antibodies and cytotoxic lymphocytes were markedly inhibited, and transplantation of their splenocytes into naive Gunn rats adoptively transferred the tolerance, indicating a role for regulatory cells. Lymphocytes from the tolerized rats hyperexpressed TGFbeta1, IL2, and IL4 upon exposure to viral antigens, whereas IFNgamma expression became undetectable. Thus, oral tolerization with adenoviral antigens permits long-term gene expression by repeated injections of recombinant adenoviruses.

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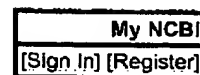
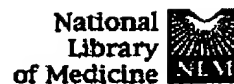
## Expression and function of recombinant endothelial nitric oxide synthase gene in canine basilar artery.

Chen AE, O'Brien T, Tsutsui M, Kinoshita H, Pompili VJ, Crotty TB, Spector DJ, Katusic ZS.

Department of Anesthesiology, Mayo Clinic, Rochester, Minn 55905, USA.

Endothelial NO synthase (eNOS) is an enzyme responsible for the production of a potent vasodilator and a key regulator of vascular tone, NO. In peripheral arteries, expression of a recombinant eNOS gene increases production of NO in the blood vessel wall. This approach appears to be a promising strategy for gene therapy of cerebrovascular disease. The major objective of the present study was to determine whether a recombinant eNOS gene (AdCMVNOS) can be functionally expressed in cerebral arteries. Replication-defective recombinant adenovirus vectors encoding bovine eNOS and Escherichia coli beta-galactosidase (AdCMVLacZ) genes, driven by the cytomegalovirus promoter, were used for ex vivo gene transfer. Rings of canine basilar artery were incubated with increasing titers of the vectors in MEM. Twenty-four or forty-eight hours after gene transfer, expression and function of AdCMVNOS were evaluated by (1) immunohistochemical staining, (2) isometric tension recording, and (3) cGMP radioimmunoassay. Transfection with AdCMVNOS resulted in the expression of recombinant eNOS protein in the vascular adventitia and endothelium, associated with significantly reduced contractile responses to UTP and enhanced endothelium-dependent relaxation to calcium ionophore A23187. Basal production of cGMP was significantly increased in the transfected vessels. The reduced contractions to UTP with increased cGMP production were reversed by a NOS inhibitor, N(G)-monomethyl-L-arginine. Contractions to UTP or production of cGMP were not affected in arteries transfected with AdCMVLacZ reporter gene. The results of the present study represent the first successful transfer and functional expression of recombinant eNOS gene in cerebral arteries. Our findings suggest that cerebral arterial tone can be modulated by recombinant eNOS expression in the vessel wall.

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**Targeting endothelial cells with adenovirus expressing nitric oxide synthase prevents elevation of blood pressure in stroke-prone spontaneously hypertensive rats.**

**Miller WH, Brosnan MJ, Graham D, Nicol CG, Morecroft I, Channon KM, Danfloy SM, Reynolds PN, Baker AH, Dominiczak AF.**

BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow G11 6NT, UK.

Local adenoviral (Ad)-mediated gene transfer to the carotid artery of the stroke-prone spontaneously hypertensive rat (SHRSP) is successful in improving endothelial function. Here we explored the potential of systemic delivery of Ad encoding endothelial nitric oxide synthase (Ad-eNOS) to prevent elevation of blood pressure in the SHRSP using both nontargeted and vector targeting approaches. Systemic administration of nontargeted Ad-eNOS failed to modify the rise in blood pressure in SHRSP when administered during the 12th week of age ( $n = 5$ ,  $P = 0.088$ ,  $F = 3.0$ ), an effect likely to result from sequestration of Ad by the liver. Rerouting Ad transduction using a bispecific antibody (anti-ACE/anti-Ad capsid, Fab9B9) that blocks Ad binding to the coxsackie and adenovirus receptor and simultaneously retargets Ad-eNOS to the angiotensin-converting enzyme resulted in efficient eNOS overexpression in the lung vasculature and a sustained hypotensive effect ( $n = 5$ ,  $P = 0.007$ ,  $F = 7.9$ ). This study highlights the importance of vector targeting to achieve therapeutic gain and represents the first such study in cardiovascular gene therapy.

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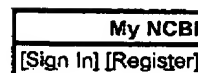
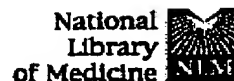
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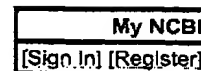
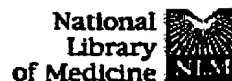
### Platelet-derived growth factor (PDGF) gene delivery for application in periodontal tissue engineering.

Giannobile WV, Lee CS, Tomala MP, Tejada KM, Zhu Z.

Department of Periodontics/Prevention/Geriatics & Center for Bio restoration of Oral Health, The University of Michigan, Ann Arbor 48109-1078, USA.  
wgian nob@umich.edu

**BACKGROUND:** A challenge in the reconstruction of periodontal structures is the targeted delivery of growth-promoting molecules to the tooth root surface. Polypeptide growth factors such as platelet-derived growth factor (PDGF) stimulate both cementogenesis and osteogenesis. Recent advances in gene therapy offer the advantage of delivering recombinant proteins to tissues for extended periods of time in vivo. **METHODS:** Recombinant adenoviral vectors encoding for the PDGF-A gene were constructed to allow delivery of PDGF transgenes to cells. The recombinant adenoviruses were assembled using the viral backbone of Ad2/CMV/EGFP and replacing GFP (reporter gene encoding green fluorescent protein driven by the cytomegalovirus promoter [CMV] within adenovirus type 2) with the PDGF-A gene. Root lining cells (cloned cementoblasts) were transduced with Ad2/PDGF-A and evaluated for gene expression, DNA synthesis, and cell proliferation. PDGF-inducible genes, c-myc and osteopontin, were also evaluated following gene delivery of Ad2/PDGF-A. **RESULTS:** The results revealed high level transduction of cementoblasts by gene transfer for 7 days as evidenced by flow cytometry and Northern blotting. Cementoblast DNA synthesis and subsequent proliferation were stimulated by Ad2/PDGF-A at levels equal to or greater than continuous rhPDGF-AA application. Strong message for the PDGF-A gene and protein as evidenced by Northern blotting and immunocytochemistry was noted. Furthermore, the potent induction of c-myc and osteopontin mRNA was found after PDGF gene delivery to cementoblasts. **CONCLUSIONS:** These findings demonstrate that gene delivery of platelet-derived growth factor stimulates cementoblast activity that is sustained above that of rhPDGF-AA application. The use of gene therapy as a mode of growth factor delivery offers a novel approach to periodontal tissue engineering.

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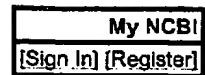
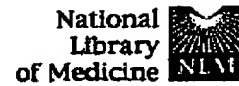
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**Adenovirus-mediated gene therapy of osteoblasts in vitro and in vivo.****Mehrra BJ, Saadeh PB, Steinbrech DS, Dudziak M, Spector JA, Greenwald JA, Gittes GK, Longaker MT.**

The Laboratory of Developmental Biology and Repair, The Institute of Reconstructive Plastic Surgery, and The Department of Surgery, New York University Medical Center, New York, New York 10016, USA.

Modulation of biological pathways governing osteogenesis may accelerate osseous regeneration and reduce the incidence of complications associated with fracture healing. Transforming growth factor beta1 (TGF-beta1) is a potent growth factor implicated in the regulation of osteogenesis and fracture repair. The use of recombinant proteins, however, has significant disadvantages and has limited the clinical utility of these molecules. Targeted gene therapy using adenovirus vectors is a technique that may circumvent difficulties associated with growth factor delivery. In this study, we investigate the efficacy of replication-deficient adenoviruses containing the human TGF-beta1 and the bacterial lacZ genes in transfecting osteoblasts in vitro and osseous tissues in vivo. We demonstrate that adenovirus-mediated gene therapy efficiently transfects osteoblasts in vitro with the TGF-beta1 virus causing a marked up-regulation in TGF-beta1 mRNA expression even 7 days after transfection. Increased TGF-beta1 mRNA expression was efficiently translated into protein production and resulted in approximately a 46-fold increase in TGF-beta1 synthesis as compared with control cells (vehicle- or B-galactosidase-transfected). Moreover, virally produced TGF-beta1 was functionally active and regulated the expression of collagen Ialpha1 (5-fold increase) and the vascular endothelial growth factor (2.5-fold increase). Using an adenovirus vector encoding the Escherichia coli LacZ gene, we demonstrated that adenovirus-mediated gene transfer efficiently transfects osteoblasts and osteocytes in vivo and that transfection can be performed by a simple percutaneous injection. Finally, we show that delivery of the hTGF-beta1 gene to osseous tissues in vivo results in significant changes in the epiphyseal plate primarily as a result of increased thickness of the provisional calcification zone.

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1: J Rheumatol. 1998 Sep;25(9):1666-73.

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**Adenovirus mediated gene delivery to the joints of guinea pigs.****Ikeda T, Kubo T, Arai Y, Nakanishi T, Kobayashi K, Takahashi K, Imanishi J, Takigawa M, Hirasawa Y.**

Department of Orthopaedic Surgery, Kyoto Prefectural University of Medicine, Japan.

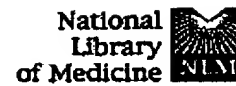
**OBJECTIVE:** To clarify in vivo applicability of adenovirus mediated gene delivery to examine a gene therapy for human joint diseases. **METHODS:** We directly injected vectors harbouring beta-galactosidase gene and transforming growth factor (TGF)-beta1 gene into the joints of Hartley guinea pigs. Expressions of delivered LacZ were examined by 5-bromo-4-chloro-3-indolyl-beta-D-galactoside staining and reverse transcription-polymerase chain reaction. The levels of TGF-beta1 that were delivered to the joint and then transferred to the joint fluid were assessed by ELISA. **RESULTS:** LacZ expression was observed in almost all synovial tissue samples and in chondrocytes on the surface of degenerated cartilage. In the other organs, expression of delivered genes was not observed. For 2 weeks following gene delivery TGF-beta1 levels in joint fluid were significantly higher than the levels in the controls for 2 weeks. **CONCLUSION:** Direct gene delivery into the joint cavity is feasible with the in vivo gene delivery method using adenovirus vector and would be clinically applicable.

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1: Gene Ther. 1996 Oct;3(10):919-26.

[Related Articles, Links](#)**Heart muscle-specific gene expression using replication defective recombinant adenovirus.****Rothmann T, Katus HA, Hartong R, Perricaudet M, Franz WM.**

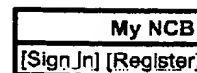
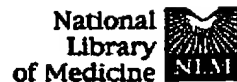
Innere Medizin III, University of Heidelberg, Germany.

Adenoviruses are a promising vector system for future gene therapy of heart muscle diseases. The promiscuous tissue tropism of adenoviruses, however, may lead to the undesirable expression of putative therapeutic genes in nontarget cells and hence to considerable safety limitations for this vector system. To restrict gene expression to cardiomyocytes we constructed an adenoviral vector (Ad-mlcLuc) in which the luciferase gene is under the control of the ventricle-specific myosin light chain-2 (mlc-2v) promoter. For controls, we constructed a recombinant adenovirus without promoter (Ad-Luc) and one with the Rous sarcoma virus (RSV) promoter (Ad-rsvLuc). Our data demonstrate that the newly established viral vector Ad-mlcLuc was specifically active in rat neonatal cardiomyocytes in vitro but not in three established cell lines. Injections of the recombinant adenoviruses into the cardiac cavity of neonatal rats resulted in myocardial specific gene expression of Ad-mlcLuc in vivo, despite the fact that viral DNA was detected by PCR at different levels in all tissues investigated. In vitro and in vivo, Ad-mlcLuc was exclusively active in cardiac muscle cells, reaching 8-9% of the RSV-induced luciferase activity. Direct injection of Ad-mlcLuc into thigh muscle gave only background luciferase activity (0.05% of Ad-rsvLuc). Therefore, in the adenoviral system, the mlc-2v promoter allows heart-specific expression of a foreign gene thus providing a promising tool for gene transfer targeted to the myocardium.

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1: Circulation. 2000 Feb 1;101(4):408-14.

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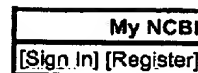
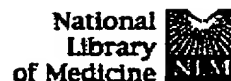
**Intracoronary adenovirus-mediated delivery and overexpression of the beta(2)-adrenergic receptor in the heart : prospects for molecular ventricular assistance.**

**Shah AS, Lilly RE, Kypson AP, Tai O, Hata JA, Phippen A, Silvestry SC, Lefkowitz RJ, Glower DD, Koch WJ.**

Departments of General and Thoracic Surgery, and The Howard Hughes Medical Institute, Duke University Medical Center, Durham, NC 27710, USA.

**BACKGROUND:** Genetic modulation of ventricular function may offer a novel therapeutic strategy for patients with congestive heart failure. Myocardial overexpression of beta(2)-adrenergic receptors (beta(2)ARs) has been shown to enhance contractility in transgenic mice and reverse signaling abnormalities found in failing cardiomyocytes in culture. In this study, we sought to determine the feasibility and in vivo consequences of delivering an adenovirus containing the human beta(2)AR cDNA to ventricular myocardium via catheter-mediated subselective intracoronary delivery. **METHODS AND RESULTS:** Rabbits underwent percutaneous subselective catheterization of either the left or right coronary artery and infusion of adenoviral vectors containing either a marker transgene (Adeno-betaGal) or the beta(2)AR (Adeno-beta(2)AR). Ventricular function was assessed before catheterization and 3 to 6 days after gene delivery. Both left circumflex- and right coronary artery-mediated delivery of Adeno-beta(2)AR resulted in approximately 10-fold overexpression in a chamber-specific manner. Delivery of Adeno-betaGal did not alter in vivo left ventricular (LV) systolic function, whereas overexpression of beta(2)ARs in the LV improved global LV contractility, as measured by dP/dt(max), at baseline and in response to isoproterenol at both 3 and 6 days after gene delivery. **CONCLUSIONS:** Percutaneous adenovirus-mediated intracoronary delivery of a potentially therapeutic transgene is feasible, and acute global LV function can be enhanced by LV-specific overexpression of the beta(2)AR. Thus, genetic modulation to enhance the function of the heart may represent a novel therapeutic strategy for congestive heart failure and can be viewed as molecular ventricular assistance.

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[www.bloodjournal.org](http://www.bloodjournal.org)**CD40-ligand (CD154) gene therapy for chronic lymphocytic leukemia.****Wierda WG, Cantwell MJ, Woods SJ, Rassenti LZ, Prussak CE, Kipps TJ.**

Division of Hematology/Oncology, Department of Medicine, and the UCSD Human Gene Therapy Program, University of California-San Diego, La Jolla, CA.

Chronic lymphocytic leukemia (CLL) cells can be made to express recombinant CD40-ligand (CD154) by transduction with a replication-defective adenovirus vector (Ad-CD154). Ad-CD154-transduced and bystander leukemia cells become highly effective antigen-presenting cells that can induce CLL-specific autologous cytotoxic T lymphocytes in vitro. This study investigated the immunologic and clinical responses to infusion of autologous Ad-CD154-CLL cells in patients with CLL. After a one-time bolus infusion of autologous Ad-CD154-transduced leukemia cells, there was increased or de novo expression of immune accessory molecules on bystander, noninfected CLL cells in vivo. Treated patients also developed high plasma levels of interleukin-12 and interferon-gamma, the magnitudes of which corresponded to absolute blood CD4(+) T-cell counts before therapy. On average, patients experienced a greater than 240% increase in absolute blood T-cell counts within 1 to 4 weeks of treatment. Moreover, treatment increased the numbers of leukemia-specific T cells, demonstrated by autologous ELISPOT assay and mixed lymphocyte reactions. These biologic effects were associated with reductions in leukemia cell counts and lymph node size. Treatment did not induce autoimmune thrombocytopenia or hemolytic anemia and no dose-limiting toxicity was observed. This approach may provide a novel and effective form of gene therapy for patients with this disease.

**Publication Types:**

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